IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	T. Takagi et al.	Attorney Docket No.:	DAISAN126511
Application No.:	10/554974	Art Unit:	1614 / Confirmation No.: 9465
Filed:	March 2, 2006	Examiner:	K.E. Weddington
Title:	SUGAR INTAKE-ABILITY ENHANCER		

DECLARATION OF DR. TOSHIYUKI TAKAGI PURSUANT TO 37 C.F.R. § 1.132

Seattle, Washington 98101

January 18, 2010

I, Toshiyuki Takagi, declare as follows.

1. I am a co-inventor of the methods described in the above-identified patent application.

I graduated from Tokyo Institute of Technology, Tokyo, Japan, in 1996, and received a doctorate degree from Tokyo Institute of Technology in 1999. My studies there related to "DSIF, a novel transcription elongation factor that regulates RNA polymerase II processivity, is composed of human Spt4 and Spt5 homologs."

I have contributed to many scientific papers. For example, I am a lead author of "Effect of pravastatin on the development of diabetes and adiponectin production," *Atherosclerosis* 2008, 196, 114-21. I am a co-author of "Synthesis and biological activity of novel alpha-substituted beta-phenylpropionic acids having pyridin-2-ylphenyl moiety as antihyperglycemic agents," *Bioorg. Med. Chem.* 2004, 12, 2419-39; "Novel benzoylpiperidine-based stearoyl-CoA desaturase-1 inhibitors: Identification of 6-[4-(2-methylbenzoyl)piperidin-1-yl]pyridazine-3-carboxylic acid (2-hydroxy-2-pyridin-3-ylethyl)amide and its plasma triglyceride-lowering effects in Zucker fatty rats," *Bioorg. Med. Chem. Lett.* 2009, Oct 29; "Novel and potent inhibitors of stearoyl-CoA desaturase-1. Part II: Identification of 4-ethylamino-3-(2-

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hydroxyethoxy)-N-[5-(3-trifluoromethylbenzyl)thiazol-2-yl]benzamide and its biological evaluation," *Bioorg. Med. Chem. Lett.* 2009, 19, 4159-66; and "Novel and potent inhibitors of stearoyl-CoA desaturase-1. Part I: Discovery of 3-(2-hydroxyethoxy)-4-methoxy-N-[5-(3-trifluoromethylbenzyl)thiazol-2-yl]benzamide," *Bioorg. Med. Chem. Lett.* 2009;19, 4151-8.

I have worked for Sankyo Company, Limited, now Daiichi Sankyo Company, Limited, ("Daiichi Sankyo") Tokyo, Japan, since 1999. My research activities at Daiichi Sankyo have included the pharmacological development of several anti-diabetes therapeutic drug candidates. While at Daiichi Sankyo, I have studied as a Visiting Researcher at Osaka University, Japan, for two years since 2004. I presently work in the Clinical Development Department at Daiichi Sankyo.

2. I understand that Claims 25, 31, and 36 of the above-identified patent application stand rejected as anticipated by Freeman et al., *Circulation* 103:357-372, January 2001 (the "Freeman reference") and that Claims 25, 31, 33, and 36 of the above-identified patent application stand rejected as unpatentable over the Freeman reference when combined with the teachings of U.S. Patent No. 5,643,868 (the "Weiner reference") and Paolisso et al., *European Journal of Clinical Pharmacology*, Vol. 40, No. 1, pp. 27-31 (1991) (the "Paolisso reference").

3. The Freeman reference describes a retroactive study of human subjects treated with pravastatin to determine if pravastatin influenced the risk of developing diabetes over time. The study concluded that pravastatin therapy significantly reduced the risk of developing diabetes in the treated group. The authors of the study speculate that three known effects of pravastatin therapy may play a role in the development of diabetes: (1) the lowering of triglycerides, (2) the anti-inflammatory properties of pravastatin, and (3) the effect of pravastatin on endothelial function.

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4. The methods described in the above-identified patent application are based on the discovery that an HMG-CoA reductase inhibitor enhances glucose uptake in warm-blooded animal cells, in particular warm-blooded animal adipocytes. The present application describes that the HMG-CoA reductase inhibitor pravastatin enhances glucose uptake into a mouse adipocyte cell line (3T3-L1). The present application further describes increased glucose uptake in adipocytes isolated from mouse strains administered pravastatin.

5. The Freeman reference does not disclose the methods described and claimed in the above-identified patent application. As mentioned above, the Freeman reference speculates that three known effects of pravastatin therapy may explain the finding that pravastatin therapy may reduce the propensity of subjects within the study to develop diabetes. However, none of these three effects is disclosed as being related to glucose uptake by adipocytes.

6. The Freeman reference further states that "there may be other direct or indirect effects of pravastatin therapy on glucose control that have yet to be unraveled." See page 361, left hand column, third full paragraph. My work and that of Dr. Iichiro Shimomura, a co-inventor of the above-identified patent application, has identified and demonstrated that pravastatin directly regulates glucose uptake by warm-blooded animal cells, including adipocytes. Therefore, our work has made a substantial contribution to the field of insulin resistance that may be useful for the treatment of diabetes and related conditions. In contrast, the Freeman reference merely speculates that pravastatin may have other effects on glucose control, without providing any data as to what those effects may be.

7. The Freeman reference does not support a conclusion that administration of pravastatin to a warm-blooded animal would necessarily enhance glucose uptake into adipocytes. The Freeman reference suggests that pravastatin may affect numerous unrelated biological processes, any one of which may correlate with for the findings of the Freeman study. However,

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the Freeman reference does not mention or even speculate that enhanced glucose uptake into adipocytes may account for the decreased risk of diabetes observed in the study.

8. The Patent Office has stated that glucose transport as described in the Freeman reference has the same characteristics as glucose uptake. See the Office Action mailed December 4, 2008. The Freeman reference mentions the effect of pravastatin on endothelial function. See third paragraph at first column on page 361 of the Freeman reference. The Freeman reference speculates that pravastatin restores endothelial function and affects glucose and insulin transport through restoration. However, there is no scientific evidence that supports this speculation. Therefore, because the Freeman reference does not disclose the function of pravastatin on enhancing glucose transport, the skilled person would not understand the function of pravastatin on enhancing glucose transport based on the Freeman reference.

In contrast, the present application demonstrates that pravastatin directly enhances insulin-induced glucose uptake into warm-blooded animal adipocytes both *in vivo* (see Example 1) and *in vitro* (see Example 2).

Furthermore, glucose transport across the endothelium is a different process than insulin-induced glucose uptake into warm-blooded animal cells such as adipocytes. Glucose transport across the endothelium refers generally to movement of glucose from capillaries into tissues. Insulin-induced glucose uptake refers to movement of glucose from the extracellular space into the selective cells in an insulin-dependent manner. Therefore, insulin-induced glucose uptake into cells and glucose transport across the endothelium do not share the same mechanisms of action.

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9. I hereby declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true and, further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Toshiyuki Takagi

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January 18, 2010

Date

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